**Episode 69: Infertility Work-Up**

Dr. Joe Chappelle: Hello everyone and welcome back. I’m Joe Chappelle and you’re listening to Episode 69 of the OB/GYN Podcast. Today, we’re going to hear from one of my favorite collaborators. Dr. Jillian Kurtz is going to walk us through the evidence-based approach to an infertility work-up. This is really aimed at generalists, and I think it does a great job of touching on all the basics. This is a patient visit that I see frequently, and I really enjoyed this review, and I hope you all enjoy it as much as I did.

Dr. Jillian Kurtz: Hi, you guys. I’m so excited to be back. I hope everyone is staying safe in this COVID-19 pandemic. For me, it meant a lot more time at home to be able to work on academic pursuits, like putting together this podcast for you guys. Today, I’m going to discuss achieving pregnancy naturally in opposite sex couples, and then going into the work-up of infertility should we fail to achieve pregnancy within the desired period of time. I would love to discuss options for same sex and transgender couples in the future, but that’s too much information for one podcast, so I had to keep the scope somewhat narrow today.

Let’s start with establishing appropriate expectations. The monthly fecundability, meaning how likely it is to get pregnant per month, is highest within the first three months, and approaches 20 to 22%. The vast majority, 80% of couples, will be pregnant within the first six months of trying. For women greater than 35, if they’re not pregnant, now is the time to start an evaluation. Now, if the woman is less than 35, it’s reasonable to keep trying for another six months, and an additional 5% of people will be pregnant without any intervention. Once they’ve been trying for a year without pregnancy, they officially meet the diagnosis of infertility. If the woman is greater than 40, we should start the work-up right away, because she is at such high risk for having challenges.

We grow up being so fearful of an accidental pregnancy, and what you learn in health class as an adolescent makes it seem like any intercourse without protection will inevitably result in pregnancy. So, a lot of women have the unrealistic expectation that once they go off birth control, they’ll get pregnant the following month. But, in reality, humans are not very efficient at this process, so let’s talk about what we can do to make getting pregnant as efficient as possible. I get asked lots of really basic questions, like, “When should we do it? How often do we have to do it? Do I have to have an orgasm? What position is best?” These are all really good questions that have been studies by researchers and have evidence-based answers. So, let’s get into it.

First and foremost, timing. There are only a certain number of days in the month that we can even get pregnant. So, when is the appropriate time to have sex? Cervical mucus acts as a sperm reservoir, and sperm can survive for several days by hanging out in this mucus, and also by adhering itself further upstream to the epithelium of the fallopian tube. There have been pregnancies reported from a single act of intercourse as long as a week prior to ovulation, but we actually consider the fertile window to be a span of six days, ending on the day of ovulation, with the highest days of conception being the two days prior to ovulation. This correlates to the time in the cycle when estrogen levels peak due to the growing follicle that results in cervical mucus that’s slippery and clear. Ovulation predictor kits measure urinary LH and can help you determine this fertile window, but they have a 7% false positive rate, especially common in PCOS women, who are living with a high LH level at baseline. So, for some women, it’s more reliable to just time intercourse based on the quality and quantity of your cervical mucus. A prospective study of almost 3,000 cycles, this was published in Human Reproduction, showed that timing intercourse by cervical mucus is more accurate than using a menstrual calendar, and having sex on a day in which cervical mucus is present is twice as likely to result in pregnancy. People go crazy over their apps that track their cycle, but sometimes just listening to your body is more beneficial. Once we’ve ovulated, the egg only has about 12 to 24 hours in which it can be fertilized before it undergoes atresia. The post-ovulatory progesterone levels produce a change in cervical mucus that prevent further entry of sperm.

I get asked a lot in the office about the frequency of intercourse. There was a study published in the New England Journal of Medicine that looked at timing and frequency of intercourse relative to ovulation. Assuming that each act of intercourse contributes independently to the chance of pregnancy, daily intercourse in the fertile window conferred the greatest chance of pregnancy. The estimated rate of conception falls from 37% to 33% with intercourse every other day, and all the way to 15% when intercourse occurred only once weekly. There’s a common misconception that frequent ejaculations decrease male fertility, that they need time to replenish the supply, so to speak. But in men with normal semen quality, sperm concentrations and motility remain normal even with daily ejaculation. And in some men with oligospermia, concentration and motility might be highest with frequent ejaculation. That being said, forced time intercourse can really get old, especially when the couple has been at this for several times in a row. The stress associated with trying to conceive can reduce sexual satisfaction and even lead to erectile dysfunction. Given that the rate of conception is only slightly higher with daily intercourse, we can appropriately advice that they have intercourse every one to two days during the fertile window, and they can decide as a couple what works best for them within that guideline.

Alright, so say you have intercourse at the appropriate time, now what? Can you get up right away to shower? Do you have to lie there supine for 30 minutes? Does it help if your feet are in the air? Well, back in the ‘60s, we discovered that the uterus functions a peristaltic pump with the ability to contract in different directions based on where’re you’re at in your cycle. At the time of menstruation, we have strong contractions in the fundo-cervical direction to help expel the menstrual blood. During the late follicular phase, we have strong contractions in the cervico-fundal direction to help with sperm transport. In 1996, Kunz et al. conducted a really interesting study where they radio labelled particles, placed them in the posterior vaginal fornix and watched through hysterosalpingo-scintigraphy their movement up the reproductive tract. Amazingly, it only took two minutes for the particles to reach the isthmic portion of the fallopian tubes. Even more fascinating is that there were a greater number of particles on the ipsilateral site of the dominant follicle. Somehow, that egg acts like a beacon, drawing the sperm near, which just blows my mind.

To put it simply, the sperm will find its way up no matter what position you’re in, and it will do it in a matter of minutes. And while it is by no means necessary for the female partner to have an orgasm in order for conception to occur, it can’t hurt. Serum levels of oxytocin are elevated in both men and women after orgasm, and as we know, oxytocin favors uterine contractions. At mid-cycle, as we just learned, these contractions are cervico-fundal in direction and would facilitate sperm progression through the reproductive tract. But the prostaglandins in the seminal fluid induce this progression as well, even in the absence of an orgasm. As a side note, water-based lubricants like KY, Astroglide and even saliva have a detrimental effect in vitro on sperm parameters, so if a lubricant is necessary, we always recommend hydroxyethylcellulose-based lubricants, like Pre-Seed or just straight mineral oil, which don’t have any adverse effects on sperm.

There is not a lot of evidence to suggest that any particular diet is more helpful than another when trying to conceive. We know that a person who is obese or underweight has a longer time to pregnancy than someone who has a healthy BMI, so maintaining a diet and exercise program that keeps you within a healthy BMI range is the best bet.

I think it’s pretty obvious that smoking has a deleterious effect on several health parameters. The ASRM committee opinion goes into great detail on the effects of smoking and infertility. In a nutshell, women who are regular smokers go through menopause, on average, one to four years earlier than non-smokers, presumably because of accelerated depletion of the follicular pool. They’re 60% more likely to be infertile, and should conception occur, have an increased risk of ectopic pregnancy and miscarriage. So, it goes without saying, smoking should be discouraged.

The effect of alcohol and caffeine consumption on fertility is a little less clear. For both, it seems as though high levels of consumption can negatively impact fertility, but moderate intake, meaning two or fewer drinks per day, doesn’t seem to be associated with any loss of fertility potential.

As states begin to legalize recreational marijuana – we’re up to 11 states so far – the issue of cannabis is becoming increasingly relevant. What we know so far is that there are cannabinoid receptors throughout the reproductive tract, which implies that it might have some effect, but studies have been conflicting. Some show no effect at all, others show it might contribute to ovulatory dysfunction, and others that it might affect sperm parameters, but the jury is still out. The larger study is the PRESTO study, which was an online, NIH funded cohort study that looked at intimate opposite sex couples from 2014 to 2017. They had over 4,000 participants and found that conception rate was the same between users and non-users of marijuana. But there are a lot of questions that still remain, like quantity and method of use, does that make a difference? We still don’t know.

Alright. So, say they’re doing all the right things for the appropriate amount of time and officially meet the criteria for infertility. A referral to REI is appropriate at this point, but most present to their general Ob/Gyn and a work-up can be initiated before you even ever have to send to an infertility specialist. ASRM and ACOG published a collaboration committee opinion in June 2019 on evaluation of the infertile couple, and it’s an awesome document if you want to refer back after the podcast.

As we should with any patient in our office, a work-up of infertility starts with an extensive history and physical exam. A diagnosis of an ovulation dysfunction can be gleaned with a menstrual history alone. Anyone with regular menses occurring every 21 to 35 days is almost necessarily ovulatory, but a confirmatory luteal phase progesterone of greater than 3 ng/mL can confirm this. If obvious menstrual disturbances exist, an etiology should be sought out, like PCOS, thyroid dysfunction, hyperprolactinemia, et cetera, because if we correct that, oftentimes ovulation will resume. If we have a woman who by history sounds ovulatory, now what test do we need to order? Well, we need to figure out three things. One, is there sperm? Two, are there eggs? And three, can they find each other?

So, starting with the first element, is there sperm? Male factor infertility is present in 40 to 50% of infertile couples, so ruling this out as early as possible is helpful. Again, starting with taking a thorough history and ordering a semen analysis. The WHO reference ranges for what is considered “normal,” is as follows. At least 1.5 mL in the ejaculate with at least 15 million sperm per milliliter, 40% motility and 4% morphology. If you’re a resident listening to this podcast, the boards love to test on these, so commit them to memory. These ranges are taken from a study that analyzed the ejaculate of 4,500 fertile men who achieved pregnancy in less than a year from 14 different countries and plotted all the components on a chart. The numbers that the WHO uses as a reference range represent the fifth centiles in this study. A poor semen analysis is not a very good predictor of a couple’s ability to achieve pregnancy, and many men still achieve pregnancy with lower parameters. But any abnormalities based on the history or the semen analysis will warrant a referral to REI or a reproductive urologist. Mild male factor infertility may be overcome with an insemination alone, but more severe abnormalities would warrant a work-up and physical exam to rule out structural problems like a varicocele or absence of the vas deferens.

Alright, moving on to the second element, are there eggs? We’ve got to figure out ovarian reserve. In its strictest sense, ovarian reserve is really an indicator of how well someone will respond to stimulation medication if they had to move forward with assisted reproduction. I.e. if we went straight to IVF, how would they respond to meds? But it has been extended to serve as a marker for quantity and quality of oocytes remaining. There are three basic ways to evaluate this. A day 2-3 FSH and estradiol level, AMH and an antral follicle count. A high day 3 FSH, meaning greater than 10 IU/L with a normal estradiol, meaning less than 60 to 80 pg/mL suggest diminished ovarian reserve. AMH is a hormone that is produced by the granulosa cells of early follicles. The levels are constant, and therefore can be drawn at any point in the menstrual cycle. AMH levels less than 1 ng/mL have been associated with poor responses to ovarian stimulation, poor embryo quality and poor pregnancy outcomes with IVF. Lastly, we have antral follicle count. This also is not cycle specific and can be done at any point throughout the menstrual cycle. With this test, we’re using transvaginal ultrasound to measure the number of follicles in the ovary, measuring 2 to 10 millimeters in size. A value less than 5 to 7 suggests diminished ovarian reserve. All of these tests are helpful in predicting response to treatment, but poor results do not necessarily imply an inability to achieve a natural pregnancy. The greatest predictor of egg quality is still the age of the female partner regardless of the ovarian reserve.

Alright, so we’ve established there are sperm and there are eggs, but are they meeting each other, are the tubes patent? Again, there are multiple ways to evaluate tubal patency, the gold standard being laparoscopy with chromopertubation. Diagnostic laparoscopy in the work-up of infertility has really fallen out of favor. It’s invasive, requires anesthesia, and there are just simpler ways to evaluate tubal patency that have acceptable sensitivity and specificity. Speaking of tests that are not simple, there was another test that was described back in the ‘60s called the PSP test, where dye was injected through the cervix into the uterine cavity. If tubes were patent, it would extravasate out into the peritoneal cavity, get absorbed, and ultimately be excreted through the renal system, changing the color of your urine. It obviously never took off, and HSG has remained our tried and true procedure for the past century, but I just thought that was interesting.

So, HSH, hysterosalpingogram, has a very high negative predictive value at 94%, meaning if the tubes appear patent on the test, then we can trust they’re truly patent, but it only has a 38% positive predictive value. It does have the advantage of helping to diagnose uterine anomalies as well as hydrosalpinges. The alternative is the hysterosalpingo contrast sonography, which is increasingly being utilized. This is, essentially, a sonohysterogram, where we infuse either foam or saline and bubbles through the transcervical catheter and simultaneously do a transvaginal ultrasound. It has a similar sensitivity and specificity as HSG, it does not involve radiation and it’s supposedly less painful for the patient, but it is operator dependent, and requires an experienced sonographer.

So, these three components are absolutely essential to the work-up: evaluate ovarian reserve, sperm and tubal patency. Of course, there are additional tests we can order. If you suspect intracavitary polyps or fibroids, a sonohysteroscopy can reveal pathology, but doesn’t need to be routinely done for all patients. We used to do endometrial biopsy to evaluate the histology, and again, not done routinely today. But keep in mind that a third of the time, the work-up is totally negative, and they fall into this annoying category called unexplained infertility. If that occurs, it really makes sense to refer them straight to a reproductive endocrinologist. We used to think that maybe giving Clomid or Letrozole empirically to women who were struggling to conceive might give them an advantage, but ASRM recently came out with an evidence-based guideline for management of unexplained infertility, and after a systematic review, determined that giving Clomid or Letrozole without also combining it with an insemination is no better than just expectant management.

Obviously, I’m biased, because I chose to make this my whole career, but I think the work-up of infertility is so fun, it’s like figuring out a puzzle. I hope you guys also thought it was fun. If you have any particular topics you want to hear about, email us and we’ll put something together. Thanks for listening, you guys. Until next time.